

**Editorial** 





# Epstein-Barr virus associated lymphoid proliferations from epidemiology to "targeted" therapies

The Epstein-Barr Virus (EBV), also called human herpesvirus 4 (HHV-4), is a virus of the herpes family, and is one of the most common viruses in humans infecting more than 90% of the world population. Childhood infection, common in developing countries, usually goes unnoticed but causes infectious mononucleosis when young adults are infected in industrialized world. The story of the discovery of the EBV is indeed connected to its oncogenic potential. Few years after Burkitt described jaw tumors in Ugandan children in 1958 later characterized as undifferentiated lymphomas, <sup>1</sup> the virus was discovered by electron microscopy in tissue cultures of Burkitt lymphoma cells.

Research during the two or three decades that followed this discovery, extended the geographic scope of Burkitt lymphoma from the high incidence of Sub-Saharan Africa, to North Africa, the Middle East<sup>2</sup> and South America as areas of intermediate incidence. A direct casual connection to nasopharyngeal carcinoma common in South East Asia was also discovered. In spite of the progress in understanding the geographic pathology of EBV-related cancers, the oncogenic potential of EBV drew relatively little interest in the United States and Europe. However, when the HIV epidemic started to sweep these continents in the eighties, the role of EBV in lymphogenesis in immune compromised patients hit home, so to speak. HIV related, post transplant and post therapy associated EBV associated lymphoproliferative disorders were intensively investigated. It became clear that EBV, though remains dormant mostly in memory B cells escaping CD8+T cell elimination in immune competent individuals, it can be reactivated in some immune compromised patients. Not only Burkitt lymphoma was associated with EBV, but several other types of T, B, NK cells, plasmablastic and Hodgkin lymphomas.3 EBV associated lymphoproliferative disorders are not uncommon in children, in the elderly, in therapy-related immune suppressed patients and in recent immigrants to the US.

Generally speaking, EBV associated lymphomas have inferior outcome compared to EBV negative counterparts. So, there is a need for novel therapeutic approaches.<sup>4</sup> This fact is not true for non-Hodgkin lymphoma only but seems to be true for Hodgkin lymphoma too.5 EBV-encoded small RNA (EBER) is the most abundant EBV viral transcript and is used as a target molecule to detect EBV infected cells in tissues by in situ hybridization. It is present in all three types of EBV dormancy. In Burkitt lymphoma, EBV nuclear antigen (EBNA) creates a proper germinal center-like micro environment for cMYC to operate. In diffuse large B cell lymphomas, EBV latent protein1 (LMP1) acts as a strong pro-proliferative and anti apoptotic oncogene. LMP1 up regulates nuclear factor kappa (NFKB) leading to proliferation. Inhibiting NFKB seems to be a very attractive approach for EBV associated lymphoma therapy. Other attractive approaches include: EBV adoptive immunotherapy, miRNA-targeted therapy and combination therapy based on EBV lytic phase induction followed by exposure of the tumor cells to anti-herpes drugs.4

Importantly, overcoming cellular senescence is strictly required for virus-driven tumors, including those associated with Epstein-Barr virus. This critical step is successfully accomplished by EBV through Volume I Issue I - 2014

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telomere reverse transcriptase (TERT) expression and telomerase activation in infected cells. There is a complex interplay between EBV and TERT/telomerase in EBV-driven tumorigenesis. Evidence accumulated so far clearly indicates that elucidation of this issue may offer promising opportunities for the design of innovative treatment modalities for EBV-associated malignancies. Indeed, several therapeutic strategies for telomerase inhibition have been developed and are being investigated in clinical trials. TERT inhibition sensitizes EBV+ lymphoma cells to antiviral through activation of EBV lytic replication is particularly promising and provides a rationale for the activation of clinical studies aimed at assessing the effects of combination therapies with TERT inhibitors and anti-virals for the treatment of EBV-associated lymphomas. In short, the six-decadelong EBV saga unveils the fact that understanding epidemiology can lead to a significant progress in cancer prevention and therapy.

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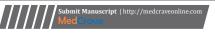
None.

## **Conflicts of interest**

Authors declare there are no conflicts of interest.

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